TABLE I. Data at Diagnosis From BCR-ABL-Positive ALL Cases*

Patient	ALL-1	ALL-2	ALL-3	ALL-4	ALL-5
Age (years)	16	37	16	19	48
Sex	F	F	F	M	M
Hemoglobin (g%)	9.0	9.0	5.0	5.0	6.0
WBC ($\times 10^3/mm^3$)	18.0	32.5	127.0	44.3	69.0
Platelets ($\times 10^3/mm^3$)	10.0	140.0	88.0	74.0	89.0
Hepatosplenomegaly	Yes	Yes	No	No	No
Mediastinal mass	No	No	Yes	No	No
FAB	L1	L2	L2	L1	L1
Immunophenotype	T-ALL	c-ALL	T-ALL	c-ALL+ My marker	c-ALL
Rearrangement	b3-a2	b2-a2	b3-a2	b2-a2	b3-a2
Karyotype		No mitosis	46,XX		

*F, female; M, male; FAB, French-American-British classification.

BCR-ABL-positive patients [4]. About half of adult ALL patients express the p190 protein produced by fusion of BCR exon 1 to ABL exon 2, and the other cases express the p210 protein, as in CML patients [7,8]. Amino terminus sequence is the only difference between p190 and p210, and both have marked tyrosine kinase activity [8]. The BCR-ABL rearrangement is associated with poor prognosis in pediatric and adult populations, and the proportion of ALL patients who are BCR-ABL-positive increases with age [2].

We studied 17 adult ALL patients using reverse transcriptase-polimerase chain reaction (RT-PCR) to detect the BCR-ABL rearrangement. There were 52.9% c-ALL, 11.8% pre-B ALL, 5.9% (1 case) c-ALL with myeloid marker, and 17.6% (3 cases) T-ALL. The rearrangement was detected in 5 patients (29.4%) (Table I): type b3-a2 in 3 cases and b2-a2 in 2 cases, without any rearrangement involving the first intron of the BCR gene. The karyotype was normal in 1 patient, and without mitosis in another patient. RT-PCR was not performed in 3 of the BCR-ABL-positive cases. Among the positive cases, there were two T-ALL (CD7 69%/CD3 21%, and CD5 95%/CD7 90%: both were negative for B lineage and myeloid markers), an unusual finding, confirmed by hybridization with a specific probe to ABL exon 2 and automatic sequencing. Westbrook et al. (1992) [3] considered that the expression of T antigens was less common in BCR-ABL-positive ALL patients, and that it never occurred in the absence of B antigens. On the other hand, many cases of T-ALL Ph-positive were described by several authors but cases of BCR-ABL-positive ALL were less frequent in the literature [9], even in studies that analyzed a great number of patients. In this study, we did not identify any case of ALL with rearrangement in the first intron of the BCR gene. It might be that all of our BCR-ABL-positive cases were de novo ALL with b2-a2 or b3-a2 rearrangement, or that some of them could represent the blastic-transformation phase of subclinical CML [10]. We conclude that, considering the probable prognostic importance, BCR-ABL rearrangement should be sought in all patients, even in T-ALL cases.

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References

1. Sandberg A, Kohono S, Wake N, Minowada J: Chromosomes and causation of human cancer and leukemia. XLII. Cancer Genet Cytogenet 2:145–174, 1980.
2. Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV: Philadelphia positive acute lymphoblastic leukemia in adults: Age, distribution, BCR breakpoint and prognostic significance. Leukemia 5:196–199, 1991.
3. Westbrook CA, Hooberman AL, Spino C, Dodge RK, Larson RA, Davey F, Wurster-Hill DH, Sobol RE, Schiffer C, Bloomfield C: Clinical significance of BCR-ABL fusion gene in adult acute lymphoblastic leukemia: A cancer and leukemia group B study (8762). Blood 80:2983–2990, 1992.
4. Kantarjian H, Talpaz M, Estey E, Ku S, Kurzrock R: What is the contribution of molecular studies to the diagnosis of BCR-ABL-positive disease in adult acute leukemia? Am J Hematol 96:133–138, 1994.
5. De Klein A, van Kessel AG, Grosveld G, Bartram CR, Hagemeijer A, Bootsma D, Spurr NK, Heisterkamp N, Groffen J, Stephenson JR: A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukemia. Nature 300:765–767, 1982.
6. Rowley JD: Identification of the constant chromosome regions involved in human hematologic malignant disease. Science 216:749–751, 1982.
7. Kurzrock R, Shtalrid M, Romero P, Kloetzer WS, Talpaz M, Trujillo JM, Blick M, Beran M, Gutterman JU: A novel c-abl protein product in Philadelphia-positive acute lymphoblastic leukemia. Nature 325:631–635, 1987.
8. Clark SS, McLaughlin J, Crist WM, Champlin R, Witte ON: Unique forms of the abl tyrosine kinase distinguish Ph1-positive CML from Ph1-positive ALL. Science 235:85–88, 1987.
9. Devaraj PE, Foroni L, Kitra-Roussos V, Secker-Walker LM: Detection of BCR-ABL and E2A-PBX1 fusion genes by RT-PCR in acute lymphoblastic leukaemia with failed or normal cytogenetics. Br J Haematol 89:349–355, 1995.
10. Kurzrock R, Gutterman JU, Talpaz M: The molecular genetics of Philadelphia chromosome-positive leukemias. N Engl J Med 319:990–998, 1988.

Hepatosplenic T-Cell Lymphoma: Sinusoidal Localization of Malignant T-Cells—A Case Report

To the Editor: Hepatosplenic T-cell lymphoma is a distinct clinicopathologic entity. It occurs at a younger age group, and patients present with hepatosplenomegaly with minimal lymphadenopathy. The feature worth stressing is the sinusoidal localization of the malignant T cells. Admixture with erythrophagocytizing benign histiocytes may be seen. Bone marrow and peripheral blood are involved later in the course of the disease.

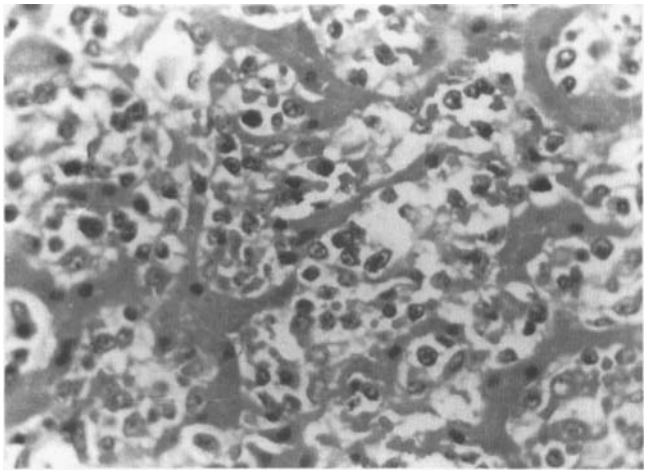

Fig. 1. Liver shows sinusoidal dilatation and packing of sinusoids by malignant T cells (H&E × 280).

This 15-year-old female presented with weight loss (14 kg), fever, epistaxis, and abdominal lump of 4 months' duration. Her liver was palpable 7 cm below the right costal margin, and the spleen was palpable 28 cm below the left costal margin. Two to three lymph nodes (1 cm each) were found enlarged in the axillary and inguinal regions. Investigations revealed hemoglobin of 5.8 g/dl, and a platelet count of 30,000/μl. The total leukocyte count was 4,200/μl with 21% immature lymphoid cells. The atypical cells were large with round-to-oval nuclei, many with prominent nucleoli, fine chromatin, and moderate amounts of cytoplasm. Many cells showed nuclear indentations. Antemortem bone-marrow aspirate was cellular and revealed 50% immature lymphoid cells of nulceated nonerythroid cells.

At necropsy, the spleen weighed 2.8 kg and was diffusely enlarged. Microscopically, the sinusoids of the red pulp were dilated and packed with malignant cells. The white pulp was atrophic. The malignant cells were medium-sized, and discretely placed with a moderate amount of cytoplasm. Most nuclei were round-to-oval with prominent nucleoli and fine chromatin. However, cells with nuclear indentation were also seen. The liver weighed 3.1 kg, and on cut section revealed a diffuse enlargement. Microscopically, marked sinusoidal dilatation and packing by similar atypical lymphoid cells were seen (Fig. 1). Postmortem bone marrow showed near total replacement by malignant cells. The lymph nodes (axillary, paraaortic, inguinal, and carinal) revealed only sinus histiocytosis with benign erythrophagocytizing histiocytes in the sinuses. Immunoperoxidase staining was done on the sections of the liver and spleen, using T (CD 45 RO), B (CD 20), and macrophage (alpha antichymotrypsin) monoclonal antibodies. The T-cell marker was strongly positive. B-cell and macrophage markers were negative. Electron microscopy was done, which further corroborated the lymphoid origin of the cells. The diagnosis was of hepatosplenic T-cell lymphoma with sinusoidal localization of malignant cells, involving the bone marrow and peripheral blood.

The revised European-American classification of lymphoid neoplasms stressed a new entity called hepatosplenic γδ T-cell lymphoma [1]. This entity was recognized by Kadin et al. in 1981 [2]. Further reports came in 1990 when Falini and Pileri studied 9 such cases [3]. They designated these cases as peripheral T-cell lymphoma associated with hemophagocytic syndrome due to the exuberant admixture of benign erythrophagocytizing histiocytes with malignant T-cells. Again in 1990, Farcet and Gaulad studied 2 such cases of hepatosplenic T-cell lymphoma with sinusoidal localization of malignant cells which expressed the T-cell receptor [4]. No erythrophagocytosis was seen in these 2 cases. The feature worth stressing in all cases is the sinusoidal localization of the malignant T-cells. The prognosis is poor.

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References

1. Harris NL, Jaffe ES: A revised European-American classification of lymphoid neoplasms: A proposal from the International Study Group. Blood 84:1361–1392, 1994.
2. Kadin ME, Kamoun M, Lamberg J: Erythrophagocytic T lymphoma: A clinicopathologic entity resembling malignant histiocytosis. N Engl J Med 304:648, 1981.
3. Falini B, Pileri S: Peripheral T cell lymphoma associated with hemophagocytic syndrome. Blood 75:434–444, 1990.
4. Farcet JP, Gaulad P: Hepatosplenic T-cell lymphoma: Sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor. Blood 75:2213–2219, 1990.

Cold Agglutinin Hemolysis Responding to Fludarabine Therapy

To the Editor: Cold agglutinin hemolysis is a hematological disorder characterized by immune (cold antibody)-mediated hemolytic anemia. Typically, these autoantibodies are most active at temperatures below 37°C. Either acute or chronic forms of the disorder may occur. The defect in the regulation of the immune response underlying the production of cold agglutinins remains unknown. The acute form of the disease is usually self-limited and may occur following infection with mycoplasma pneumoniae. A chronic form may be found in persons with an underlying lymphoproliferative disorder. In other individuals, no evidence of an underlying disease can be found, and these cases are termed idiopathic. Patients with a mild form of the disease may achieve control of their symptoms by avoiding cold exposure. Therapy with alkylating agents, such as chlorambucil or cyclophosphamide, is necessary for more severe forms of the disease. Splenectomy and corticosteroids are not usually effective. Spontaneous remissions and exacerbations do sometimes occur.

This letter describes a patient with idiopathic cold agglutinin disease who initially responded to cyclophosphamide-containing chemotherapy but subsequently became refractory to this agent. Treatment was changed to fludarabine, a purine nucleoside analog which resulted in a prolonged clinical remission. This is the first report of clinical activity of fludarabine in idiopathic cold agglutinin disease.

A 75-year-old male was referred with a 6-week history of intermittent chest pain and dyspnoea on exertion. He had had no recent fever, sweats, or weight loss. There was no history of respiratory infection. He was not on any medications, was a nonsmoker, and did not drink alcohol.

Physical findings showed the patient to be afebrile with a pulse of 70 beats per min, a respiratory rate of 15 per min, and blood pressure of 140/80. There was no palpable lymphadenopathy. Examination of the heart, lungs, and abdomen found no abnormalities. Laboratory examination in-